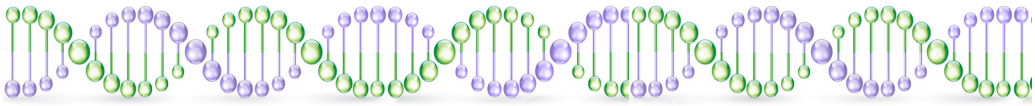
Information Sheet



Li Fraumeni syndrome and the TP53 gene

Li Fraumeni syndrome is a rare, inherited cancer syndrome caused by mutations affecting the TP53 gene. It is associated with a very high risk of cancer including soft tissue sarcoma, osteosarcoma, premenopausal breast cancer, brain tumours, adrenocortical carcinomas and leukaemia. These cancers may occur in childhood or young adulthood.

Li Fraumeni syndrome gets its name from the doctors, Dr Frederick Li and Dr Joseph Fraumeni. In 1969, Dr Li and Dr Fraumeni described four families in which the children had had multiple cancers. The term Li Fraumeni syndrome was first used in 1982 in a scientific article describing 2 different families who also had multiple children with young onset cancer.

What causes Li Fraumeni syndrome?

Li Fraumeni syndrome is caused by a mutation affecting the TP53 gene. The TP53 gene is a quality assurance gene which makes the p53 protein. If the TP53 gene isn't working, cells with mistakes in their DNA are permitted to keep dividing, allowing cancers to develop.

Li Fraumeni syndrome is usually caused by an inherited (germline) mutation. In 10 to 20% of people with Li Fraumeni syndrome, the mutation has occurred "de novo". That is, the mutation only occurred when that particular egg or sperm was made or in the first few cell divisions after fertilisation. The mutation was not present in your parents but can be passed on to your children.

How common is Li Fraumeni syndrome?

Until recently there were less than 500 known families with Li Fraumeni syndrome world wide. Now, with TP53 being included on most cancer gene panels, the prevalence of Li Fraumeni syndrome, and Li Fraumeni-like syndrome, is though to be much higher, maybe affecting 1 in 20,000 families.

How is Li Fraumeni syndrome diagnosed?

To determine who should have a genetic test for Li Fraumeni syndrome, the Chompret criteria were developed. The Chompret criteria for an individual includes 2 different cancers from the Li Fraumeni syndrome tumour spectrum, with the first diagnosed before 46 years.

For a familial presentation, one cancers need to have occurred before 46 years in one person and before 56 years or multiple primary tumours at any age in the second, closely related blood relative.

Cancers associated with Li Fraumeni syndrome include:

- sarcoma of the bone or soft tissue
- brain tumours
- premenopausal breast cancers (especially if HER2 positive)
- adrenocortical carcinomas
- acute leukaemia

A diagnosis of Li Fraumeni Like syndrome may be made when the Chompret criteria are almost, but not quite, met.

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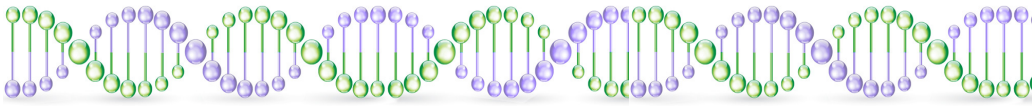

How is Li Fraumeni syndrome managed or treated?
Li Fraumeni syndrome can't be cured. Management focuses on early diagnosis through screening, which starts at a young age, and sometimes surgery.

Cancer risk is very high with more than 80% of people with Li Fraumeni syndrome getting at least one cancer. The cancers may occur in childhood. The chance of developing cancer for a woman with Li Fraumeni syndrome is 50% before she turns 30. For men, it is around 50% by age 40.

Management guidelines for men and women with Li Fraumeni syndrome include:

- an annual whole-body MRI
- annual brain MRI
- annual dermatological review
- colonoscopy every 1 to 2 years
- bilateral mastectomies for women at age 25.

For women who carry a TP53 mutation, bilateral mastectomies (removal of the breast tissue) are strongly recommended. This is because of the very high lifetime risk of breast cancer (>80%) coupled with a need to avoid even low dose radiation, either for screening or for treatment, if possible. Bilateral risk reducing mastectomies reduces the lifetime risk of breast cancer to <2% (which is significantly lower than the population-based risk of 10%).

If a woman elects to pursue increased breast screening instead, breast screening should commence at age 25 with annual breast MRI. In Australia, this screening is Medicare-funded.

Individuals with Li Fraumeni syndrome should avoid unnecessary radiation, should not smoke, should follow sun-sense guidelines and should maintain a healthy lifestyle that includes a diet high in fruits and vegetables and moderate daily exercise.

What if a TP53 mutation is detected in the blood but the family history doesn't fit with Li Fraumeni syndrome?
Genetic testing uses the DNA from white cells (collected via a blood or saliva sample). If a mistake has occurred in the TP53 gene of the stem cells that made those white cells, a TP53 mutation may be detected on a genetic test even though that person does not have Li Fraumeni syndrome. This is called Clonal Haematopoiesis of Indeterminate Potential (or CHIP for short).

CHIP is more common in older patients (because there will be more mistakes in all their cells, including the ones in the bone marrow) and in patients where the bone marrow may have been damaged (through radiation or chemotherapy). While most patients with CHIP don't need to worry, for some it can be a sign of an active cancer or leukaemia.

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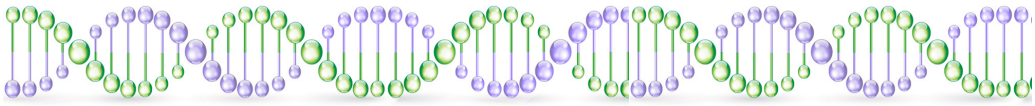

Will my children have Li Fraumeni syndrome?
There is a 50% chance of a person who carries a germline TP53 mutation, whether male or female, passing the mutation to their son or daughter.

Using a technique called preimplantation genetic diagnosis (PGD) in the setting of in vitro fertilisation (IVF) it is possible to prevent the familial TP53 mutation being passed on to future generations.

Does this sound like you or your family?
Have you had multiple cancers or a very young onset cancer? Has a TP53 mutation been detected in a blood relative or does the family meet the Chompret criteria? Genetic testing is available and may be Medicare funded.

Make an appointment with Dr Hilda High at Sydney Cancer Genetics. It is a confidential opportunity to discuss your personal and family history of cancer and genetic testing can be organised, if needed.

More information is available on our website, including links to the following:

- Support groups for people with Li Fraumeni exist in both Australia and New Zealand. See the ANZ branch of the international Li Fraumeni Association for information, including current research trials.
- The Cancer Genetics section of the Cancer Institute's eviQ website provides up-to-date Australian-based management guidelines
- The US National Library of Medicine website has more information about this syndrome.

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